PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Pediatric post-discharge mortality in developing countries: A systematic review
AUTHORS	Nemetchek, Brooklyn; English, Lacey; Kissoon, Niranjan; Ansermino, J; Moschovis, Peter; Kabakyenga, Jerome; Fowler-Kerry, Susan; Kumbakumba, Elias; Wiens, Matthew

VERSION 1 – REVIEW

REVIEWER	Patricia Pavlinac, PhD MS University of Washington, Seattle, WA, USA
REVIEW RETURNED	23-May-2018

GENERAL COMMENTS	This systematic review addresses an important and under-represented global health topic, post-discharge mortality. The review represents a follow-up to a previously published systematic review conducted by the same group which was the first to collate post-discharge mortality rates among children in low-resource settings. I have very few comments as this review is well-written and appropriately conducted. The few comments I do have are listed below: I understand the authors' decision to focus solely on describing the studies only as opposed to conducting analytics. That being said, it does seem that there is an opportunity to conduct a simple meta-analysis of the post-discharge mortality rates (recognizing the limitation that studies report these based on variable follow-up times) and explicitly examine sources of heterogeneity (diagnosis, length of follow-up, time-period study was conducted) using meta-regression. Such an analysis may provide statistical backing to claims such as malaria/anemia having lower PDM rates than other diagnoses. This however is only a suggestion and the authors' decision not to do this is understandable. The search is reported to have covered articles published through July 18, 2017 and according to the search in the Appendix, it appears the search was run on July 18, 2017. Given it may take time to index new publications in MEDLINE, it might be worthwhile to run the search again with publication date of up to July 18, 2017 to ensure no articles that were in fact published before July 18 but were not yet indexed and therefore missed by the search. The definition of admission to hospital is not entirely clear and may be important for interpretation of the mortality estimates across studies. For example, the GEMS study (Kotloff et al) included children who presented to care with diarrhea but who weren't necessarily hospitalized and it's unclear if the mortality rates

	reported in this review were among all those children who presented to care, or only among those who ended up being hospitalized. Mixing of the two populations may lead to underestimation of the true post-discharge rate since one would assume children who presented to care but weren't actually admitted would have better outcomes. Having a more explicit definition of hospital admission, such as an over-night stay in the facility, might be useful (albeit may not be possible given the review authors are limited by how admission was defined in the primary studies). In terms of other assessments of bias, could also consider funnel plots to evaluate potential publication bias. Funnel plots should be do-able with proportions (such as post-discharge mortality rates). Table 3. The columns of "PD Re-hospitalized" and "PDM" present the rates of re-hospitalization and death over follow-up, respctively. Given that some studies have multiple follow-up times (as reflected in column "Follow-up Times"), is it safe to assume that the estimates presented in the table reflect the cumulative rate as of the last follow-up point? If so, would suggest adding this to the footnote. Table 6. Reddy et all: The OR associated with not receiving anti-TB medication (2.50 95% CI: 0.03-2.00) may be a typo because the OR is not contained within the confidence interval and seems to be in an entirely different direction from the OR associated with not receiving anti-TB medication for the 8-week death assessment. Table 7. Growth parameters in Kotloff study all represent the same parameter (enrollment HAZ). I suspect the difference between the three rows is age group, but this is not indicated in the table. HIV-infection appears to be an important risk factor for post-discharge mortality (among others). Given HIV-exposure, even in the absence of infection, is an established risk factor for mortality and malnutrition, and that there is a growing population of HIV-exposed, uninfected children in sub-Saharan Africa, I'm curious if any studies reported on HIV-exposure as a risk factor for PDM?

REVIEWER	Andrew C Argent University of Cape Town and Red Cross War Memorial Children's Hospital, South Africa
REVIEW RETURNED	27-May-2018

GENERAL COMMENTS	General Comments Throughout the paper the authors have used a variety of terms such as "developing countries", "resource limited settings", "low income countries" etc. In fact, entry criteria for the systematic review was "countries with a low human development index (HDI). While there is a complexity to resource limitations and many other aspects of national development, quality of life etc, I would encourage the authors to consider maintaining a consistency and specificity of terminology throughout the paper. To take another perspective 'Resources must everywhere and always be allocated between alternative ends: a resource used for one purpose is not available for another.' (Maynard and Bloor). Finally the term "resource limited" implies a binary world where you have or you don't have. That is not an accurate reflection of the world, and in fact there is a wide range of resources (even within categories of need) and the use / utilization of resources is related to factors such a political environments, freedom etc (which the authors have alluded to by

	using the human development index). Overall this is an important study which adds substantially to the paediatric literature. Specific Comments Title The comment about “resource limited settings” above may be applicable to the title as well. Would it be a problem to refer to PDM in low HDI countries? Introduction The introduction reads well and provides an excellent basis for the study. Methods Inclusion criteria The authors reference 2 reports on Human Development (2011 and 2016). It is notable that a number of countries (e.g. Kenya and Pakistan) that were categorised as low HDI in 2011 are now no longer in that category in 2016, but those countries are still included within the study. The authors need to clarify exactly which definition of low HDI they are applying in this particular review. Results All Admissions, Including Unspecified Infectious Admissions The comment is made that “parasitaemia was protective …”. I wonder if it would be more accurate to say that parasitaemia was associated with lower post discharge mortality. It seems unlikely that having a parasitic infection is actually “protective”. The comment: “Anthropometric factors (including MUAC, weight-forage, weight-for-height, and height-for-age z-scores), hypoxia, respiratory rate, jaundice, hepatomegaly, and Blantyre coma scale rating were physiological factors found significant” does not read well. It may make sense to split up the components of the sentence. I assume the authors mean that all these factors were significantly associated with increased or decreased mortality. Respiratory infection I wonder how best to deal with “associations” between post discharge mortality and various parameters. The authors have made statement that various parameters are associated with mortality. However, the data is show in categorical form (e.g. Hb<7 vs > 7). It is being in the wrong category that is associated with the mortality not really the parameter (in fact the relationship between the parameter and the outcome is inverse in many situations). Discussion In the discussion the authors state that “Sepsis, therefore, as the final common pathway for the majority of infectious disease related deaths, is a helpful framework within which to explore pediatric post-discharge mortality and to develop interventions.” At best they can only say that it may be. Earlier in the results they have pointed out that there is no data available on the cause of death (or the nature of dying) in the children who die following hospital discharge. I am concerned that by suggesting the focus on sepsis the authors are pre-empting the gathering of accurate data on how and why children die following hospital discharge. Is the priority actually a focus on sepsis, or is possibly on post hospital follow-up, nutrition, access to

	care, maternal education etc etc? In the discussion the authors refer to the high rate of loss of follow up in the studies included in the review. That data is present in table 1, but it might be useful to highlight that data in the text related to the nature of the studies. It is concerning on some levels that the data has some homogeneity over a period of nearly 40 years. Perhaps the authors could discuss the issues of whether earlier studies should be included in the systematic review. The inclusion of studies possibly should be related to whether the countries in question have implemented immunization programmes (and the range of those programmes) or other interventions that might have been expected to affect child mortality (both pre and post hospital admission). It would be intriguing to consider the baseline mortality rate in children in those communities who have not suffered a hospital admission. The data that increased numbers of admssions are associated with increased mortality suggests that children who have been admitted to hospital are at increased risk, but the baseline data would be useful in considering this data. Conclusions The conclusions are appropriate

REVIEWER	Patricia Bastero Texas Children's Hospital. Baylor College of Medicine. Houston, TX USA
REVIEW RETURNED	27-May-2018

GENERAL COMMENTS	1. Page 21 line 39: it should say "poor" instead of porr 2. Provide a table summarizing the findings by each of the disease studied here (anemia/malaria, respiratory infection, diarrhea or malnutrition) including the studies that report all of the following: a) percentage of PDM (compared to in hospital death) within 1,2 and/or 6 months post-discharge, and b) the risk factors associated to PDM. It would be a good summary reflecting the most valuable data currently available in the literature, and it would be very helpful for future prospective studies.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Patricia Pavlinac, PhD MS
Institution and Country: University of Washington, Seattle, WA, USA
Competing Interests: None declared

This systematic review addresses an important andunder-represented global health topic, post-discharge mortality. The review represents a follow-up to a previously published systematic review conducted by the same group which was the first to collate post-discharge mortality rates among children in low-resource settings. I have very few comments as this review is well-written and appropriately conducted. The few comments I do have are listed below:

1. I understand the authors' decision to focus solely on describing the studies only as opposed to conducting analytics. That being said, it does seem that there is an opportunity to conduct a simple meta-analysis of the post-discharge mortality rates (recognizing the limitation that

studies report these based on variable follow-up times) and explicitly examine sources of heterogeneity (diagnosis, length of follow-up, time-period study was conducted) using meta-regression. Such an analysis may provide statistical backing to claims such as malaria/anemia having lower PDM rates than other diagnoses. This however is only a suggestion and the authors' decision not to do this is understandable.

Thank you for this important comment. We agree that a meta-regression approach may be a suitable means of exploring the effect of various heterogeneous factors (diseases population, duration of follow-up, etc.) on post-discharge mortality. Our decision to not include any formal pooling of data came primarily out of our perspective that a more descriptive approach, rather than a statistical approach, would better highlight the overarching issue of this manuscript. This is, namely, that post-discharge mortality is a crisis in pediatric global health.

Despite this, we do have intentions of more formal statistical modelling. Our group is currently conducting a large prospective cohort study in Uganda. Using this data, our previous cohort data as well as data that we will attempt to procure through more extensive collaboration, we wish to conduct an individual patient-level data meta-analysis (that includes time-to-event data). Through this approach, we can achieve what you have suggested in this comment, namely a more robust understanding of influencing disease states as well as a better understanding of changing risk and convalescence following discharge.

2. The search is reported to have covered articles published through July 18, 2017 and according to the search in the Appendix, it appears the search was run on July 18, 2017. Given it may take time to index new publications in MEDLINE, it might be worthwhile to run the search again with publication date of up to July 18, 2017 to ensure no articles that were in fact published before July 18 but were not yet indexed and therefore missed by the search.
Thank you for identifying the possibly mis-leading wording in regards to the search strategy and identified articles. The manuscript has been revised in order to read "*Articles published <u>and indexed</u> between Jan 1, 2012 and July 18, 2017 were identified using the MEDLINE and EMBASE databases within the OVID platform…*". We believe that this should clarify that the search strategy was indeed conducted on July 18th, and that those articles indexed in the databases prior to that date were therefore identified.
3. The definition of admission to hospital is not entirely clear and may be important for interpretation of the mortality estimates across studies. For example, the GEMS study (Kotloff et al) included children who presented to care with diarrhea but who weren't necessarily hospitalized and it's unclear if the mortality rates reported in this review were among all those children who presented to care, or only among those who ended up being hospitalized. Mixing of the two populations may lead to underestimation of the true post-discharge rate since one would assume children who presented to care but weren't actually admitted would have better outcomes. Having a more explicit definition of hospital admission, such as an over-night stay in the facility, might be useful (albeit may not be possible given the review authors are limited by how admission was defined in the primary studies).
Thank you for identifying the ambiguity around what defines a hospital admission for our specified population. Indeed, we did attempt to define admission as at least an overnight stay, but did not necessarily require a study to have defined admission in this way (or any other way). We believe that all of our other studies did, however, focus primarily on in-patients who were admitted at least overnight. However In the GEMS study, we believe that in fact you are correct. While they use the term discharge several times in this paper, upon closer review we realized that not all subjects were indeed admitted. This was an oversight by our team, and to maintain consistency we have removed this article from our list of included studies. Thank you for pointing out this error.
4. In terms of other assessments of bias, could also consider funnel plots to evaluate potential publication bias. Funnel plots should be do-able with proportions (such as post-discharge mortality rates).
Thank you for suggesting a funnel plot as a possible method to evaluate publication bias. The post-discharge mortality rates identified by the studies included were simple numbers or percentages, with no confidence intervals, standard deviation, or standard error. Such information is necessary in order to construct a funnel plot, and so is thus not feasible for this study. It is our intent, to eventually add to the literature with additional data, and perhaps form

additional collaborations so that we can attempt an individual patient-level-data meta-analysis, which would then allow us to construct funnel plots.

5. Table 3. The columns of “PD Re-hospitalized” and “PDM” present the rates of re-hospitalization and death over follow-up, respectively. Given that some studies have multiple follow-up times (as reflected in column “Follow-up Times”), is it safe to assume that the estimates presented in the table reflect the cumulative rate as of the last follow-up point? If so, would suggest adding this to the footnote.
   Thank you for identifying, correctly, that those specified columns as well as others (i.e. IPM, loss to follow up) are cumulative rates as of the last follow-up point. A footnote has been added in regards to the required columns to further clarify.
6. Table 6. Reddy et all: The OR associated with not receiving anti-TB medication (2.50 95% CI: 0.03-2.00) may be a typo because the OR is not contained within the confidence interval and seems to be in an entirely different direction from the OR associated with not receiving anti-TB medication for the 8-week death assessment.
   Thank you for your identification of the typing error- it has now been corrected to “0.25 (0.03, 2.00)” in the table.
7. Table 7. Growth parameters in Kotloff study all represent the same parameter (enrollment HAZ). I suspect the difference between the three rows is age group, but this is not indicated in the table.
   Thank you for your comment indicating that age group had not been specified in Table 7 regarding growth parameters. This study has been removed due to not fully fulfilling the PICOS criteria based upon population, as importantly noted in another comment.
8. HIV-infection appears to be an important risk factor for post-discharge mortality (among others). Given HIV-exposure, even in the absence of infection, is an established risk factor for mortality and malnutrition, and that there is a growing population of HIV-exposed, uninfected children in sub-Saharan Africa, I’m curious if any studies reported on HIV-exposure as a risk factor for PDM?
   You have identified a very important issue, and one which our research group is now examining in more detail in a large post-discharge pediatric cohort. Unfortunately, this information was not present in this group of studies. This SLR has reported all risk factors for PDM that each individual study themselves identified.

Reviewer: 2

Reviewer Name: Andrew C Argent
Institution and Country: University of Cape Town and Red Cross War Memorial Children's Hospital, South Africa
Competing Interests: None declared

General Comments: Throughout the paper the authors have used a variety of terms such as “developing countries”,“resource limited settings”, “low income countries” etc. In fact, entry criteria for the systematic review was “countries with a low human development index (HDI). While there is a complexity to resource limitations and many other aspects of national development, quality of life etc, I would encourage the authors to consider maintaining a consistency and specificity of terminology throughout the paper. To take another perspective ‘Resources must everywhere and always be allocated between alternative ends: a resource used for one purpose is not available for another.’ (Maynard and Bloor). Finally the term “resource limited” implies a binary world where you have or you don’t have. That is not an accurate reflection of the world, and in fact there is a wide range of resources (even within categories of need) and the use / utilization of resources is related to factors such a political environments, freedom etc (which the authors have alluded to by using the human development index). Overall this is an important study which adds substantially to the paediatric literature.

Specific Comments

1. Title: The comment about “resource limited settings” above may be applicable to the title as well. Would it be a problem to refer to PDM in low HDI countries?
   Thank you for this comment and your earlier reflection on this important issue. We agree that we have rather haphazardly mixed a variety of terms in this paper, and that there is a need for

improved consistency in terminology. For the purposes of this paper, we will choose to use the term developing country throughout, except with regards to the systematic search. We will choose to define a developing country as those having a low HDI, as this allows us to use the appropriate MeSH and Emtree terms within the databases that were searched as a part of this SLR.

Introduction: The introduction reads well and provides an excellent basis for the study.

Thank you.

2. Methods: Inclusion criteria: The authors reference 2 reports on Human Development (2011 and 2016). It is notable that a number of countries (e.g. Kenya and Pakistan) that were categorised as low HDI in 2011 are now no longer in that category in 2016, but those countries are still included within the study. The authors need to clarify exactly which definition of low HDI they are applying in this particular review.
Thank you for correctly identifying the fact that two reports were used- the current (2016) HDI, as well as that used in 2011, when the previous SLR was done. Table 1 does indicate our study population and which countries were included: "…defined as those countries currently (2016) classified by the United Nations Development Program (UNDP) as having a low Human Development Index plus those countries included previously (2011) as having a low Human Development Index." The same information was also added under the Methods: Search Strategy so thatimportant country inclusion criteria also is stated within the written body of the paper. Although it may technically be more appropriate to exclude some countries in this update that were previously included, we believe that important lessons and observations can be gleaned form including a consistent group of countries between the initial review and this update.
3. Results: All Admissions, Including Unspecified Infectious Admissions: The comment is made that "parasitaemia was protective …". I wonder if it would be more accurate to say that parasitaemia was associated with lower post discharge mortality. It seems unlikely that having a parasitic infection is actually "protective".
Thank you for identifying the possibly misleading wording around the use of protective. The sentence has been changed as follows: "Parasitemia was found to be associated with lower PDM compared to other diagnoses in two studies, with the third study showing lower PDM compared to diarrhea, anemia and other less common diagnoses."
4. The comment: "Anthropometric factors (including MUAC, weight-forage, weight-for-height, and height-for-age z-scores), hypoxia, respiratory rate, jaundice, hepatomegaly, and Blantyre coma scale rating were physiological factors found significant" does not read well. It may make sense to split up the components of the sentence. I assume the authors mean that all these factors were significantly associated with increased or decreased mortality.
Thank you for identifying the poor flow of this sentence. It has been reworded as follows: "Anthropometric factors (including MUAC, weight-for-age, weight-for-height, and height-for-age z-scores), hypoxia, respiratory rate, jaundice, hepatomegaly, and Blantyre coma scale rating were all associated with a statistically significant increase in the probably of PDM"
5. Respiratory infection: I wonder how best to deal with "associations" between post discharge mortality and various parameters. The authors have made statement that various parameters are associated with mortality. However, the data is show in categorical form (e.g. Hb<7 vs > 7). It is being in the wrong category that is associated with the mortality not really the parameter (in fact the relationship between the parameter and the outcome is inverse in many situations).
We agree that perhaps additional technical clarity could improve the reporting of results. A tension exists in this regard as adding extensive technical clarity reduces the overall readability of the paper, perhaps making it slightly pedantic. In thissection, however, we have attempted to add some additional technical clarity. The following has been added to the paragraph on respirator infection: "Although individual studies differed in regards to whether risk factors were measured continuously, categorically, or dichotomously, it is clear that the directionality of certain risk factors such as low hemoglobin, low or high temperature, and low MUAC continue to be associated with higher PDM in pediatrics admitted for respiratory illness."
6. Discussion: In the discussion the authors state that "Sepsis, therefore, as the final common pathway for the majority of infectious disease related deaths, is a helpful framework within

which to explore pediatric post-discharge mortality and to develop interventions." At best they can only say that it may be. Earlier in the results they have pointed out that there is no data available on the cause of death (or the nature of dying) in the children who die following hospital discharge. I am concerned that by suggesting the focus on sepsis the authors are pre-empting the gathering of accurate data on how and why children die following hospital discharge. Is the priority actually a focus on sepsis, or is possibly on post hospital follow-up, nutrition, access to care, maternal education etc etc?
Thank you for identifying a possibly misleading sentence, and its potential implications for the reader's understanding of this SLR. The sentence indicated in the comment has been revised to state that it "may be" instead of "is".

7. In the discussion the authors refer to the high rate of loss of follow up in the studies included in the review. That data is present in table 1, but it might be useful to highlight that data in the text related to the nature of the studies.
Thank you for identifying the fact that data reflecting the high rates of loss to follow-up was not included in the write-up itself. The following sentence has been revised: "Many studies included in this review had high losses to follow-up (ranging between 0 and 39.3%)…"

8. It is concerning on some levels that the data has some homogeneity over a period of nearly 40 years. Perhaps the authors could discuss the issues of whether earlier studies should be included in the systematic review. The inclusion of studies possibly should be related to whether the countries in question have implemented immunization programmes (and the range of those programmes) or other interventions that might have been expected to affect child mortality (both pre and post hospital admission).
Thank you for identifying the pertinent fact that some of the studies included were conducted many years ago. We agree that time is an important cause of heterogeneity and certainly may be an important factor affecting the rate of post-dischargemortality. That being said, this by no means the only cause of important heterogeneity (substantially differing length of follow-up, disease populations, resources available between different countries and within countries, etc.). The significant heterogeneity seen is indeed the primary reason that we decided not to pool the data. While we certainly agree that limiting the eligibility of studies to only those conducted within the past one to two decades, we believe that the general paucity of data on pediatric post-discharge mortality justifies the more generous inclusion criteria with regards to study date. Indeed, as the reviewers have pointed out, this is a relatively neglected area of research with limited data and thus we believe that retaining the full evidence base during this early stage of evidence generation is important. As further (and better) evidence in generated, we believe that future systematic reviews (and meta-analyses) should indeed limit analysis to more pertinent time periods.

9. It would be intriguing to consider the baseline mortality rate in children in those communities who have not suffered a hospital admission. The data that increased numbers of admissions are associated with increased mortality suggests that children who have been admitted to hospital are at increased risk, but the baseline data would be useful in considering this data.
We agree with this comment completely. An understanding of community-level risk would certainly be helpful in contextualizing both re-admission and mortality data. We look forward to future opportunities to collect such data so that we can further elucidate the basic epidemiology of this important public health issue.

10. Conclusions: The conclusions are appropriate

Reviewer: 3

Reviewer Name: Patricia Bastero
Institution and Country: Texas Children's Hospital. Baylor College of Medicine. Houston, TX USA
Competing Interests: None declared

1. Page 21 line 39: it should say "poor" instead of porr
Thank you, the mistake has been corrected.

2. Provide a table summarizing the findings by each of the disease studied here (anemia/malaria, respiratory infection, diarrhea or malnutrition) including the studies that report all of the following: a) percentage of PDM (compared to in hospital death) within 1,2 and/or 6 months post-discharge, and b) the risk factors associated to PDM. It would be a good summary reflecting the most valuable data currently available in the literature, and it would be very helpful for future prospective studies.
Thank you for this comment. We believe that much of the information you are requesting is indeed included in the tables of this manuscript. Specific comparisons, such as a consistent reporting of the % of post discharge deaths at particular time points, is unfortunately not available in all studies, which is why such data is not included in the existing tables. Our best attempt to capture this data was our final column in Table 3 (PDM statistics), were we report the percentage of children who died following discharge at specific time points. We did our best to find the data-points common to most studies and include them here. Indeed, the tables that we do have are an attempt to distill all of the pertinent data from each included study into an easy-to-read tabular format. Unfortunately, the between study heterogeneity in report precludes any significant additions to existing tables.

VERSION 2 – REVIEW

REVIEWER	Patricia Pavlinac University of Washington, Seattle, WA, USA
REVIEW RETURNED	10-Aug-2018

GENERAL COMMENTS	The authors have adequately addressed my comments.

REVIEWER	Andrew Argent Professor and Head, Department of Paediatrics and Child Health, University of Cape Town and Red Cross War Memorial Children's Hospital Rondebosch Cape Town South Africa
REVIEW RETURNED	31-Jul-2018

GENERAL COMMENTS	Many thanks for the responses to comments from the Reviewers. I am happy with the changes made.